Women’s Health Research: 
Moving Forward

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ORWH Mission

- Enhance, stimulate, and expand efforts to improve the health of women through biomedical and behavioral research, *across NIH*
- Examine the role of sex/gender in health and disease, *across NIH*
- Promote recruitment, retention, reentry, and advancement of women in biomedical careers
NIH Office of Research on Women’s Health

- Founded in 1990
- 1991: Women’s Health Initiative
- 1993: NIH mandate to include women and minority groups in clinical research
- 2014: NIH focal point for research on sex/gender influences on health

... Benefits girls, women, boys, men
NIH in 2014: Beyond Inclusion
Sex/Gender Influences on Health and Disease

Preclinical studies | Toxicology | Phase I, II, III Clinical Trials

Basic | Healthy Women, Men, Girls, Boys | Clinical

Cell, Animal Studies | Education | Sex-Specific Data Analyses

Health Care | Health Policy | Sex-Specific Reporting
Thank You, NIDA!

- Sustained interest in sex/gender research, ORWH collaboration
- Women & Sex/Gender Differences Research Group
- PA: Women & Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R01, R21, R03)
- Three currently funded SCOR programs
- College on Problems of Drug Dependence
  - NIDA Women & Sex/Gender Junior Investigator Travel Awards

“Today, gender-related research is integrated throughout NIDA’s entire portfolio. This research extends from basic molecular and cellular studies to clinical and epidemiologic studies and is grouped into four major areas: etiology, consequences, prevention, and treatment and services. Through this research, we are learning more and more about differences between women and men in the origins of drug abuse, the consequences of drug abuse and addiction, and the factors that influence drug abuse relapse and recovery.”
NIDA-Funded SCOR Publications

Sex Differences in Guanfacine Effects on Drug Craving and Stress Arousal in Cocaine-Dependent Individuals
Helen C Fox3, Peter T Morgan1 and Rajita Sinha2

Stability of smoking status in the US population: a longitudinal investigation
Andrea H. Weinberger1,2,3, Corey E. Pilver4, Carolyn M. Maze5,6 & Sherry A. McKee1,2,3

Smoking and mental illness in the US population.
Smith PH1, Maze CM, McKee SA

Creating Dynamic Images of Short-lived Dopamine Fluctuations with lp-ntPET: Dopamine Movies of Cigarette Smoking
Evan D. Mone1,2,3,4, Su Jin Kim1,2, Janna M. Sullivan1,2,3,4, Shuo Wong1,2, Marc D. Normandin7, Cristian C. Constantinescu8, Kelly P. Congreve1,2,3

Yohimbine administration and cue-reactivity in cocaine-dependent individuals
Megan M. Moran-Santa Maria, Almea McRae-Clark, Nathaniel L. Baker, Vinu V. Ramakrishnan, Kathleen T. Brady

Smoking topography and abstinence in adult female smokers
Erin A. McClure *, Michael E. Saladin, Nathaniel L. Baker, Matthew J. Carpenter, Kevin M. Gray

Sex differences in methamphetamine seeking in rats: Impact of oxytocin
Brittney M. Cox, Amy B. Young, Ronald E. See, Carmela M. Reichel *

Well-Being and the Risk of Depression under Stress
Faren Grant1, Constance Guille2, Srijan Sen3

Stress-Induced Cocaine Craving and Hypothalamic-Pituitary-Adrenal Responses Are Predictive of Cocaine Relapse Outcomes
Rajita Sinha, PhD; Miguel Garcia, MS; Prashni Pullawat, PhD; Mary Joanne Keck, MD; Bruce J. Roussel, MD
NIDA Administrative Supplements (2013, 2014)

2013
• Mechanisms of Nicotine Reinforcement
• Assess the Effects of Environmental Tobacco Smoke on Neurodevelopment
• Drug Abuse Vulnerability: Mechanisms and Manifestations
• Neuronal Substrates of Cocaine Reward
• Development of the Basal Telencephalic Limbic System
• Human Methamphetamine Vaccine: Translational Avante Garde Award

2014
• Characterizing a Cue-Vulnerable Pharmacoresponsive Endophenotype in Smokers
• Gender Differences in Responses to Caffeine in Children and Adolescents
• Prenatal and Environmental Tobacco Smoke Exposure: Effects on Child Regulation
• Fetal and Infant Neurobehavioral Effects of Maternal Buprenorphine Treatment
• International Collaborative of Prospective Studies of HIV and Hepatitis in Injection Drug Users
• SCOR on Sex and Gender Factors Affecting Women’s Health (supplement)
• Midbrain Neural Circuit Elements That Underlie Cue-Reward Associations
• Genetic Influences on Inhibitory Control and Cocaine Sensitivity
• Systems Genetic Analysis of Methamphetamines Motivational Effects in a Mouse Advanced Intercross Line
• Neural Mechanisms of Cognitive-Behavioral Therapy in Cocaine Dependence
Smoking

Tobacco use is the leading cause of preventable disease and death in the United States and worldwide it carries a substantial health burden. Smoking is an unhealthy habit for both genders, but women and men experience different health risks, and they respond differently to techniques designed to help them quit. Here are some examples:

Alcohol Use

Drinking alcohol is a common activity in most cultures around the world, for both women and men. However, while drinking in moderation may be considered generally safe, alcohol abuse poses many risks to a woman’s health. For example, although men are more likely to drink alcohol than are women, and men often drink more and more frequently, women are more vulnerable to some of alcohol’s harmful effects. These effects are based on both gender- and sex-based factors, and they include differences in metabolism. In addition, alcohol use by women is also linked to many other physical and psychosocial health issues, such as unprotected sex, illicit drug use, and intimate partner violence. Here are some of the facts about women and alcohol use:

Prescription Painkiller Abuse

Women in America are dying from prescription-drug overdoses at unprecedented rates. Most of these deaths are caused by opioids, painkillers that are chemically similar to heroin and that have similar effects in the body and can be highly addictive. Examples include OxyContin, Percocet, and Vicodin. Research has shown that males and females do not respond in similar ways to opioids. Here are some facts about sex- and gender-based difference in prescription painkiller abuse.

Depression

Gender plays an important role in mental health disorders like depression, which is common but underdiagnosed. Epidemiological research shows that females are more likely than males to develop not only depression, but also eating disorders, panic disorder, and post-traumatic stress disorder. Here are some sobering facts about depression in women:
NIH plans to enhance reproducibility

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

Instead, a complex array of other factors seems to have contributed to the lack of reproducibility. Factors include poor training of researchers in experimental design; increased emphasis on making provocative statements rather than presenting technical details; and publications that do not report basic elements of experimental design. Crucial experimental design elements that are all too frequently ignored include blinding, randomization, replication, sample-size calculation and the effect of sex differences. And some scientists reputedly use a 'secret sauce' to make their experiments work — and withhold details from publication or describe them only vaguely to retain a competitive edge. What hope is there that other scientists will be able to build on such work to further biomedical progress?
NIH Takes Steps to Address Sex Differences in Preclinical Research

May 14, 2014

Over the past two decades, we have learned a great deal about how men and women respond differently to medications. This knowledge came after a concerted effort in the early 90s to increase the number of women in NIH-funded clinical research. Today, just over half of NIH-funded clinical research participants are women. Unfortunately, experimental design in cell and animal research has not always followed suit. An over-reliance on male animals, and neglect of attention to the sex of cells, can lead to neglect of key sex differences that should be guiding clinical studies, and ultimately, clinical practice. NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women’s Health, and me in the Nature Comment below.

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

Director’s Page

Filling the Gaps: NIH Enacts New Policies to Address Sex Differences

Posted May 14, 2014

Today in Nature, National Institutes of Health (NIH) Director Dr. Francis Collins and I announce that NIH will be requiring applicants to report their cell and animal inclusion plans as part of preclinical experimental design. By developing this policy, we are promoting a balanced approach to addressing male and female differences in cells and animals — just as we did years ago with women and men in NIH-funded clinical trials.
Males and Females in Preclinical Research: The Landscape

- Congressional interest and inquiries
  - Research for All Act (Jim Cooper, D-TN, Cynthia Lummis, R-WY)
  - Rosa DeLauro (D-CT), Nita Lowey (D-NY) report language
  - Briefing to enhance understanding (July 2014)

- Developing NIH policies for deliberate approach to considering sex in preclinical research:
  - Animals, tissues, cells?
  - Implementation plan in development

- Journal editors and publishers guidelines
  - Increasingly reference requirements to report sex
Where Are We Now?

- Science is driving this change: Increasing published evidence of differences in female, male biology
- We know sex matters, but we don’t know when, where, and how
- Studying both sexes will help answer those questions
- Public trust: As a federal agency, NIH must be committed to understanding physiology and disease in both sexes
- The payoff: Studying both sexes will enrich biological knowledge
Postcards from the Field

“Sex differences are often insignificant.”

“Females are inherently more variable because of their estrous cycles.”

- Research does not support these ideas
- Significant differences in female, male biology/physiology/health
- Male-specific sources of variability > variation from estrous factors
- Female rodents can be studied without costly estrous monitoring
  - Studying only one sex limits generalizability of findings
Sources of Variability

“The underrepresentation of female mice in neuroscience and biomedical research is based on the assumption that females are intrinsically more variable than males and must be tested at each of four stages of the estrous cycle to generate reliable data. Neither belief is empirically based. In a meta-analysis of 293 articles, behavioral, morphological, physiological, and molecular traits were monitored in male mice and females tested without regard to estrous cycle stage; variability was not significantly greater in females than males for any endpoint and was substantially greater in males for several traits. Group housing of mice increased variability in both males and females by 37%. Utilization of female mice in neuroscience research does not require monitoring of the estrous cycle. The prevalence of sex differences at all levels of biological organization, and limitations in generalizing findings obtained with males to females, argue for the routine inclusion of female rodents in most research protocols.

Accounting for Sex in Animals

- Rigor, generalizability, and utility
  - Broad phenotypic screen of 472 knock-out lines
    - Validated assays, relevant to therapeutic areas
    - All animals screened at the same age, same order of assays
  - “Eight homozygous mice (equally divided between males and females) per assay… as we were most interested in seeing effects shared by the sexes.”
    - Results reported for M/F aggregated, M alone, and F alone
  - One of many approaches to account for sex as a biological variable

Cell Death is Influenced by Biological Sex

- Male cells programmed for necrosis, female cells programmed for apoptosis
- Estrogen treatment of male mice induced apoptosis to levels similar to that in female mice, inhibited necrosis
- Male, female responses to stress due to inherent differences in inflammatory necrosis susceptibility?
- Higher % of nephritis in men w SLE compared to in women w SLE; male sex risk factor for progression to renal failure

- Implications for treatments that target cell death pathways
Sex and Research Using Cells

- Incorporating consideration of sex here has unique challenges
  - Authentication of cell lines, genomic instability…

- Sex of origin knowable for cells derived from tissues, primary cells/cultures
  - Easy to record, report

- Increasingly required by journals, e.g. *Endocrinology*
  “…all manuscripts … must indicate the sex of animals used, or in the case of primary cells or cultures, the sex of the animal from which they were derived.”

- Reveal biological phenomena -- > understanding mechanisms, processes
  - Findings could go undetected, misunderstood w/o consideration of sex as a basic biological variable
Materials and Methods

Describe techniques, cell/animal models used (including species, strain, and sex), and lists of reagents, chemicals, and equipment, as well as the names of manufacturers and suppliers, including URLs for those supplies obtained online, so that your study can be most easily replicated by others. For studies involving humans, the sex and/or gender of participants must be reported. Also in this section, describe the statistical methods that were used to evaluate the data. If clinical trials were used, a statement of registration is required; also, for all investigations involving humans or animals, a statement of protocol approval from an IRB or IACUC, or an equivalent statement, must be included (see Guiding Principles for Research Involving Animals and Human Beings). All animal or human studies must contain an explicit statement that the protocols were submitted to, and approved by, an institutional review board or committee or that the protocols were performed under a license obtained from such a committee, board, or governing office.
Journal Policies

Endocrinology

Experimental Biology

Journal of Bone & Joint Surgery

Circulation

American Journal of Preventive Medicine

Nature

The Lancet

CMAJ

American Physiological Society

JACC

NIH - National Institutes of Health

Office of Research on Women's Health
Studying Both Sexes in Preclinical Research: To Date

- Specialized Centers of Research on Sex Differences (SCOR) program: FY 2002 to present (ORWH, NIDA, NICHD NIAMS, NIDDK, NIA, NIMH, FDA)
- ORWH administrative supplement program funds PIs to add sex/gender to current scope of grants — FY 2013 to present (ORWH, trans-NIH)
- IC efforts:
  - NIA Interventions Testing Program
  - IC sex differences RFAs
- Sex Differences in NIH Research Coordination Group, convened May 2014
  - Kathy Hudson and Janine Clayton
- Trans-NIH Sex Differences Working Group, established June 2014
  - Sally Rockey and Janine Clayton, co-chairs
  - RFI — September 2014
1. The Basic Science and the Biological Basis for Sex- and Gender-Related Differences
   - Understanding the Importance of Sex and Gender in Biomedical Research
   - Legislative Process Framework
   - Cell Physiology
   - Developmental Biology
   - Pharmacodynamics and Pharmacokinetics
   - Clinical Applications of Genomics

2. Sex and Gender Differences in Health and Behavior
   - Clinical Research Methodology
   - Endocrine Effects on Immunity
   - Drug Therapeutics during Pregnancy
   - Understanding the Importance of Sex and Gender in Mental Health
   - Autoimmunity, Autoimmune Disease, and Sex Bias
   - Sex and Gender Differences in Irritable Bowel Syndrome

3. The Influence of Sex and Gender on Disease Expression and Treatment
   - Sexual Dimorphism in Metabolic Bone Disorders
   - Cardiovascular Disease in Women: A Focus on Heart Failure
   - Sex and Gender Differences in Pulmonary Function and Health
   - The Neural Basis of Sex Differences in Pain
   - Sex Differences in Substance Abuse and Treatment

*CME or CPE credit can be awarded to eligible candidates who successfully complete Courses 1, 2, or 3
https://sexandgendercourse.od.nih.gov/
Save the Date!

- Advisory Committee on Research on Women’s Health (Sept 24, 2014)

- Methods and Techniques for Integrating the Biological Variable Sex in Preclinical Research Workshop (Oct 20, 2014)

- Interdisciplinary Women’s Health and Sex Differences Research Symposium (Nov 6, 2014)
  - Dr. Nora Volkow, keynote speaker
Causal Factors and Interventions Affecting Women in Biomedical Careers

- Senior leadership support for women’s career advancement is essential
  - Hiring, sponsorship, promotions, awards
- Unconscious bias is real, but it can be measured and changed
- Culture affects career satisfaction and performance, and it too can be measured and changed
- Mentor networks are more effective than mentor dyads
- Institutional flexibility policies are under-recognized and under-used, in part due to ingrained academic culture and lack of leadership buy-in

The Women of Color Research Network

- Social media site for everybody interested supporting the development of a diverse scientific workforce
- Facilitates interaction and collaboration between students, researchers, and policy makers
- Provides information, networking, mentoring, and career development opportunities for women of color in biomedical careers

http://www.wocrn.nih.gov/

~ 1,100 members and growing
Connecting the Dots: The Research Continuum

Basic Research & Trials
Preclinical Research
Clinical Research & Trials
Regulatory Review (if needed)
Clinical Practice

Cell models, samples of human or animal tissues, computer-assisted testing, animal models
Healthy volunteers and patients

THANK YOU!